Chiral Phosphinites Derived from α-D-Glucofuranose and α-L-Idofuranose. A Comparison to Chiral Phosphines in Asymmetric Hydrogenation[1]

Thomas H. Johnson* and G. Rangarajan

Department of Chemistry, Kansas State University, Manhattan, Kansas 66506

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Two chiral phosphinites and two chiral phosphines, which are derivatives of α-D-glucofuranose and α-L-idofuranose, were prepared and used as ligands in rhodium-catalyzed asymmetric hydrogenations. Six substrates were studied. Unlike phosphinites prepared from α-D-glucopyranose, the phosphinites prepared in this study were effective in inducing asymmetry in the hydrogenations of atropic acid and α-methylcinnamic acid. The phosphinites were frequently better chiral modifiers than phosphines when an acetamido group was not present in the substrate.

The asymmetric hydrogenation of prochiral olefins has been an active area of research during the past decade.[2-4] The most common approach has involved a metal-catalyzed reduction where the metal has been modified with an optically active phosphine. The optical activity of the phosphine has been due either to an asymmetrically substituted phosphorus or to asymmetry in the carbon structure attached to the phosphorus.[4] The most common substrates have been α-(acylamino)acrylic acids. In fact, one of the success stories of asymmetric chemistry has been the achievement of 95% or greater enantiomeric excesses in the hydrogenation of some α-(acylamino)acrylic acids.

Perusal of the literature reveals, however, that while chemists can now effect a significant amount of asymmetric induction in the hydrogenation of some α-(acylamino)acrylic acids, their efforts often fall short when either or both a carboxylic acid or an acetamido group is lacking in the substrate. In an attempt to improve upon this apparent debility of chiral phosphines, Hayashi[5] explored the use of a chiral phosphinite, *d-trans*-BDPCP, in asymmetric hydrogenations. He found that he could obtain products containing a greater enantiomeric excess than those obtained from (-)-DIOP-mediated reactions if the substrates did not contain an acetamido or carboxylic acid moiety. However, when these latter moieties were present, (-)-DIOP-mediated reactions produced products of higher enantiomeric excess.

We recently prepared[1] the chiral bis(phosphinite) camphinite and compared it to its bis(phosphine) analogue camphos. We found that camphinite was a better chiral modifier than camphos in asymmetric hydrogenation reactions when the substrates were olefinic esters. Conversely, the camphos ligand gave products of higher enantiomeric excess when the substrates contained an acetamido or carboxylic acid moiety. However, camphinite was not very effective in inducing asymmetry in many of the products. In an attempt to find more effective phosphinites for asymmetric hydrogenation, we have explored the preparation of bis(phosphinites) from carbohydrates. We report here the preparation and use of two of these bis(phosphinites). In addition, we have prepared the analogous bis(phoshines) and offer a comparison of these with the bis(phosphinites).

Table I. Asymmetric Hydrogenation of Prochiral Olefins Using Chiral Ligands 3, 4, 6, and 8

substrate	% ee 3[a]	6[a]	8[b]	4[b]
α-acetamidocinnamic acid	54	54	56	40
methyl α-acetamidocinnamate	41	35	27	24
atropic acid	36	17	8	27
methyl atropate	17	10	6	12
α-methylcinnamic acid	45	48	61	54
α-acetamido-4-acetoxy-3-methoxycinnamic acid	67	65	37	36

[a] Products were of the *S* configuration. [b] Products were of the *R* configuration.

Table II. Asymmetric Hydrogenations with Glucophinite and $(COD)_2Rh_2Cl_2$

substrate	% ee	isomer
α-acetamidocinnamic acid	8.2[a]	*R*
methyl α-acetamidocinnamate	3.4[b]	*R*
atropic acid	2.1[a]	*R*
methyl atropate	0[b]	*R*
α-methylcinnamic acid	7.1[a]	*R*
methyl α-methylcinnamate	2.3[b]	*R*

[a] Performed in benzene-EtOH (1:1) at 60 °C and 20.4 atm of hydrogen for 24 h. All hydrogenations were quantitative. [b] Performed in benzene-EtOH (1:1) at 100 °C and 68 atm of hydrogen for 48 h in order to effect complete hydrogenation.

Results and Discussion

We prepared the two bis(phosphinites) glucophinite (**4**) and idophinite (**6**) from 3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose (**1**) which in turn can be readily prepared by literature procedures[6] from glucose.

(1) For our previous paper on the preparation and use of chiral phosphinites see: Johnson, T. H.; Pretzer, D. K.; Thomen, S.; Chaffin, V. J. K.; Rangarajan, G. *J. Org. Chem.* **1979**, *44*, 1878.

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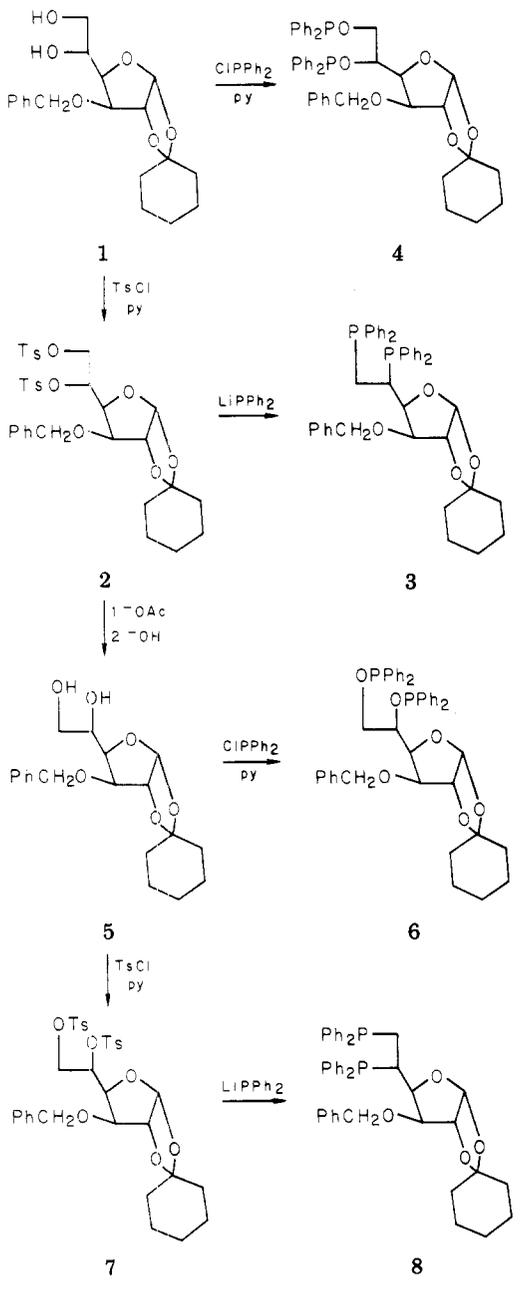
(4) Selected list of examples: Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445. Knowles, W. S.; Sabacky, M. J.; Vineyard, B.D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567. Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *Ibid.* **1977**, *99*, 5946. Horner, L.; Siegel, H; Buthe, H. B. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942. Dang, T. P.; Kagan, H. B. *Chem. Commun.* **1971**, 481. Kagan, H. B.; Dang. T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429. Gelbard, G.; Kagan, H. B.; Stern, R. Tetrahedron **1976**, *32*, 233. Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353. Morrison, J. D.; Burnett, R. E.; Aguiar, A. M.; Morrow, C. J.; Phillips, C. *J. Am. Chem. Soc.* **1971**, *93*, 1301. Morrison, J. D.; Masler, W. F. *J. Org. Chem.* **1974**, *39*, 270. Fryzuk, M. O.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262; *Ibid.* **1978**, *100*, 5491. King, R. B.; Bahos, J.; Huff, C. D.; Marko, L. *J. Org. Chem.* **1979**, *44*, 1729.

(5) Hayashi, T.; Tanaka, M.; Ogata, I. *Tetrahedron Lett.* **1977**, 295.

(6) Landor, S. R.; Miller, B. J.; Tatchell, A. R. *J. Chem. Soc. C* **1966**, 1822.

0022-3263/80/1945-0062$01.00/0

Scheme I



The analogous bis(phosphines) glucophos (8) and idophos (3), were also prepared from this intermediate. The synthesis of these four compounds is outlined in Scheme I.

These four ligands were employed in the asymmetric hydrogenation of the six substrates shown in Table I. The hydrogenations were carried out in THF at room temperature employing the cationic complex [(3, 4, 5, or 8)-Rh(COD)]BF_4 at 1 atm of hydrogen. The reactions were run for 1 h and resulted in complete reduction in all instances. The enantiomeric excess obtained from each reduction is given in Table I.

Historically, both neutral and cationic rhodium complexes have been explored in tandem with chiral modifiers as catalysts for asymmetric hydrogenation.[4] We have examined the use of the neutral $(COD)_2Rh_2Cl_2$ and glucophinite (4) under standard conditions previously used for the hydrogenation of olefinic acids and esters. We have chosen six substrates for this study. Two of the substrates contain an acetamido moiety while the other four do not. Three of the substrates are olefinic acids while the other three are their corresponding methyl esters. The results of these hydrogenations are given in Table II.

Table III. Asymmetric Hydrogenations with [(Glucophinite)Rh(COD)]BF_4[a]

substrate	% ee	isomer
α-acetamidocinnamic acid	40	*R*
methyl α-acetamidocinnamate	24	*R*
atropic acid	27	*R*
methyl atropate	12	*R*
α-methylcinnamic acid	54	*R*
methyl α-methylcinnamate	20	*R*

[a] Performed in THF at 25 °C and 1 atm of hydrogen for 1 h. All hydrogenations were quantitative.

Table IV. Asymmetric Hydrogenation of α-Acetamidocinnamic Acid with [(Glucophinite)Rh(COD)]Y in THF and EtOH[a]

	% ee[b]	
anion (Y)	THF	EtOH
BF_4^-	40	30
PF_6^-	32	30
BPh_4^-	30	35
ClO_4^-	36	28

[a] Performed at 25 °C and 1 atm of hydrogen for 1 h. [b] All products were of the *R* configuration. All hydrogenations were quantitative.

These six substrates were also hydrogenated with the cationic complex [(glucophinite)Rh(COD)]BF_4 and the results of these reductions are given in Table III. It is apparent from comparing the results of the two tables that this latter, cationic, catalyst system is quite superior to the catalyst system prepared from the neutral complex and 4. It should be pointed out, however, that these differences in realized enantioselectivity are probably not manifested only in the difference between a cationic and neutral rhodium complex. The use of the cationic complex allows for considerably lower pressures and temperatures, and increasing evidence is now mounting in support of the notion that lower pressures and temperatures have a positive influence upon asymmetric induction.[7] The more drastic conditions for the neutral complex were necessary in order to effect complete hydrogenation of the substrates. Hence, the improved enantiomeric excesses obtained from the use of the cationic complexes may in a very large part be due to the lower operating pressures and temperatures needed to effect complete hydrogenation. From a practical standpoint the cationic complexes also required only 1 h for complete conversion of the substrates whereas the neutral complexes required 24–48 h to effect a quantitative conversion. As the objective in asymmetric hydrogenation is to obtain the greatest amount of asymmetric induction, it is more important that the cationic complexes give products of higher enantiomeric excess than it is to determine the source of this increased enantioselectivity.[8]

Solvent effects have been explored by a number of workers[4] and the enantiomeric excesses obtained have changed from solvent to solvent. Additionally, workers have employed cationic complexes associated with different anions. In order to determine the effect of various anions and solvents upon the reaction, we explored the asymmetric hydrogenation of α-acetamidocinnamic acid with BF_4^-, PF_6^-, BPh_4^-, and ClO_4^- as the anions in both THF and EtOH solvents. The results are given in Table IV.

The greatest enantiomeric excess, 40%, was obtained when tetrafluoroborate was the anion and THF was the

(7) Ojima, I.; Kogure, T.; Yoda, N. *Chem. Lett.* **1979**, 495.
(8) This statement is meant only in a relative and not absolute sense.

Table V. Effect of Temperature upon the Asymmetric Hydrogenation of α-Acetamidocinnamic Acid in [(Glucophinite)Rh(COD)]BF_4-Catalyzed Hydrogenations

t, °C	% ee	isomer
25	40[a]	R
0	52[a]	R
−78	10[b]	R

[a] Performed in THF at 1 atm of hydrogen for 1 h. Hydrogenations were quantitative. [b] Performed at 1 atm of hydrogen for 3 h in order to effect complete hydrogenation.

solvent. The lowest enantiomeric excess, 28%, was obtained with perchlorate as the anion in ethanol. Interestingly, the order of greatest influence by an anion is not the same in both solvents. The order in THF was $BF_4^- > ClO_4^- > PF_6^- > BPh_4^-$ while in ethanol the order was $BPh_4^- > BF_4^- = PF_6^- > ClO_4^-$. The source of these effects is not clear at this time but the effect appears to be a very real one. The wrong choice of anion in THF could result in as much as a 10% reduction in enantiomeric excess. In ethanol this difference could be a 7% reduction in enantiomeric excess.[9]

Temperature, as mentioned above, can also have an effect upon the reaction. Using the [(glucophinite)Rh(COD)]BF_4 system in THF at 1 atm of hydrogen, we found that lowering the temperature from 25 to 0 °C resulted in an increase from 40% to 52% enantiomeric excess. The reductions were still complete within 1 h when this lower temperatrure was used. When we lowered the temperature to −78 °C, however, the reaction became sluggish and took nearly 3 h to effect complete reduction. Additionally, the entantiomeric excess obtained at −78 °C was only 10%. The results are summarized in Table V.

This study would indicate that the most desirable conditions for employing glucophinite in asymmetric hydrogenation would involve the use of the cationic rhodium complex with tetrafluoroborate as the anion in THF at 0 °C.

Several interesting results have been obtained from this study. First, glucophinite is a better chiral modifier than idophinite when the substrates do not contain an acetamido moiety. However, when the acetamido functionality is present, then idophinite is definitely superior to glucophinite. Second, idophinite is competitive with idophos (3) in inducing asymmetry in three of the six entries in Table I. Interestingly, two of these entries contain an acetamido moiety. Previously phosphine ligands had been superior to phosphinites in the asymmetric hydrogenation of substrates containing the acetamido functionality. Third, glucophinite is a substantially better chiral modifier than its analogue glucophos when the substrate is atropic acid or methyl atropate. Fourth, previously phosphinites derived from glucopyranoses were ineffective in the asymmetric hydrogenation of substrates which did not contain an acetamido moiety.[10] Even Hayashi's ligand *d-trans*-BDPCP was ineffective in the asymmetric hydrogenation of atropic acid. Here, both phosphinites were effective chiral modifiers and the 27% and 54% enantiomeric excesses obtained from the reduction of atropic acid and α-methylcinnamic acid, respectively, with glucophinite represent the highest published values of asymmetric induction for these substrates due to a chiral bis(phosphinite).

(9) These are absolute values. The relative differences are 25% and 20%, respectively. Thus, the differences are indeed large.
(10) Cullen, W. R.; Sugi, Y. *Tetrahedron Lett.* **1978**, 1635.

The two bis(phoshinites) are easy to prepare from inexpensive, optically active starting materials. We are continuing to explore the preparation and use of other phoshinites prepared from aldohexofuranoses. In addition we are exploring variations on the glucofuranose and idofuranose systems. Our overall goal is to develop a chiral bis(phosphinite) which is an effective chiral modifier in asymmetric hydrogenation for a wide range of substrates.

Experimental Section

The ^1H NMR spectra were obtained on a Varian T-60 spectrometer, using tetramethylsilane as an internal standard in $CDCl_3$–Me_2SO-d_6 (1:1). Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. Optical rotations were obtained from an ETL-NPL 143A automatic polarimeter. All of the carboxylic acid substrates were purchased or prepared by literature procedures. The methyl esters were prepared by standard diazomethane reactions on the acids. The preparation of the phosphinites and the hydrogenation mixtures was performed in a Vacuum Atmospheres drybox. The phosphines were prepared and stored under nitrogen. THF was distilled from sodium–benzophenone under nitrogen. The diol 1 was prepared according to literature procedures.[6]

3-*O*-Benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose Ditosylate (2). To a 500-mL Erlenmeyer flask containing 200 mL of freshly distilled pyridine (from BaO) at 0 °C were added 8.0 g (0.024 mol) of 1 and 8.8 g (0.046 mol) of *p*-toluenesulfonyl chloride. The Erlenmeyer flask was stoppered and refrigerated for 5 days. The resultant solid was removed by filtration. The filtrate was poured into 600 mL of ice water and then extracted with five 100-mL portions of $CHCl_3$. The chloroform extract was washed with 100-mL portions of 5% aqueous potassium bisulfate until the pyridine odor was no longer evident. The chloroform solution was then washed once with 100 mL of water, separated, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resultant oil was taken up in methanol, and 11.5 g (76%) of product crystallized upon cooling: $[\alpha]^{25}_D$ −37.8° (*c* 0.6, $CHCl_3$); ^1H NMR δ 0.9–1.3 (m, 10 H), 2.5 (s, 6 H), 3.4–3.9 (m, 8 H), 6.2 (d, 1 H), 7.2–7.4 (m, 13 H).

Idophos (3). To a 1-L, three-necked, round-bottomed flask equipped with a 250-mL addition funnel, reflux condenser, and mechanical stirrer were added 200 mL of THF and 4.4 g (0.017 mol) of triphenylphosphine followed by 0.23 g (0.034 mol) of lithium. The stirred solution was warmed to 40–45 °C until all of the lithium dissolved. Then, 1.6 g (0.017 mol) of freshly distilled *tert*-butyl chloride was added dropwise to destroy phenyllithium. The solution was brought to a quick reflux and then cooled with an ice water–salt bath. Then, 10 g of 2 in 100 mL of THF was added dropwise over a period of 1 h to the cold, stirred solution. After the addition was completed, the solution was stirred at room temperature for 2 h. Deoxygenated water (100 mL) was added and the THF was distilled from the solution. The residue was extracted with 100 mL of freshly distilled, deoxygenated benzene. The benzene layer was separated and dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resultant oil was crystallized from deoxygenated ethanol to afford 1.8 g (17%) of the product: mp 104–108 °C; $[\alpha]^{25}_D$ +54.2° (*c* 0.6, $CHCl_3$); ^1H NMR δ 0.8–1.3 (m, 10 H), 2.4–3.1 (m, 3 H), 3.3–3.9 (m, 5 H), 6.2 (d, 1 H), 7.1–7.4 (m, 25 H).

Glucophinite (4). To a 500-mL Erlenmeyer flask containing 100 mL of THF, 7.0 g (0.02 mol) of 1, 3.2 g of pyridine, and a magnetic stirring bar was added, dropwise, 4.4 g (0.04 mol) of chlorodiphenylphosphine. The reaction was stirred for 12 h and then filtered, and the filtrate was evaporated in vacuo to give a viscous oil which slowly solidified after 5 days. The crude yield was nearly quantitative and the product was used without further purification: mp 87–92 °C; $[\alpha]^{25}_D$ −21.5° (*c* 0.4, $CHCl_3$); ^1H NMR δ 0.9–1.4 (m, 10 H), 3.3–3.8 (m, 8 H), 6.2 (d, 1 H), 7.1–7.5 (m, 25 H); IR (CCl_4) 1060 (POC) cm^{-1}.

3-*O*-Benzyl-1,2-*O*-cyclohexylidene-α-L-idofuranose (5). To a 500-mL, round-bottomed flask were added 10 g (0.017 mol) of 2, 12 g of potassium acetate, and 100 mL of dry DMF. The solution was refluxed, with stirring, for 48 h, cooled, and diluted with 50 mL of water and 50 mL of ether. The layers were separated and the aqueous layer was extracted with four 50-mL

portions of ether. The combined ethereal extracts were washed with three 50-mL portions of water, separated, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The crude product thus obtained was refluxed for 10 h with 4 g of potassium hydroxide dissolved in a solution composed of 50 mL of water, 50 mL of THF, and 5 mL of ethanol. The solution was cooled, evaporated to a volume of 40 mL, and then diluted with 10 mL of water. The solution was neutralized with 50 mL of 6 N HCl and then extracted with two 50-mL portions of ether. The ether extracts were washed once with 10-mL of water and once with 10 mL of 5% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to give a viscous oil. Distillation of the oil afforded 4.2 g (78% from **2**) of the product: bp 175–180 °C (0.005 torr); $[\alpha]^{25}_D$ +53.2° (*c* 0.5, $CHCl_3$).

Idophinite (6). This compound was prepared by the same procedure used for the preparation of glucophinite except the diol **5** was used in place of the diol 1: mp 103–105 °C; $[\alpha]^{25}_D$ +78.4° (*c* 0.6, $CHCl_3$); ^1H NMR δ 0.9–1.2 (m, 10 H), 3.4–3.9 (m, 8 H), 6.2 (d, 1 H), 7.1–7.4 (m, 25 H); IR (CCl_4) 1020 (POC) cm^{-1}.

3-*O*-Benzyl-1,2-*O*-cyclohexylidene-α-L-idofuranose Ditosylate (7). This compound was prepared by the same procedure used for the preparation of ditosylate **2** except the diol **5** was used in place of the diol 1: $[\alpha]^{25}_D$ +89.2° (*c* 0.5, $CHCl_3$); ^1H NMR δ 0.9–1.2 (m, 10 H), 2.5 (s, 6 H), 3.6–4.2 (m, 8 H), 6.2 (d, 1 H), 7.1–7.4 (m, 13 H).

Glucophos (8). This compound was prepared by the same procedure used for the preparation of idophos except the ditosylate **7** was used in place of the ditosylate **2**: mp 162–165 °C; $[\alpha]^{25}_D$ +112° (*c* 0.4, $CHCl_3$); ^1H NMR δ 0.9–1.2 (m, 10 H), 2.3–2.9 (m, 3 H), 3.4–3.8 (m, 5 H), 5.2 (d, 1 H), 7.2–7.5 (m, 25 H).

General Procedure for the Reduction of the Olefinic Acids. To a 250-mL hydrogenation vessel were added 150 mL of THF, 0.1 mmol of $[Rh_2(COD)_2][BF_4]_2$,[11] and 0.3 mmol of phosphinite or phosphine. Then, 0.6 mmol of Et_3N and 10 mmol of the olefinic acid were added. The magnetically stirred solution was hydrogenated in a conventional apparatus at room temperature and 1 atm of hydrogen. All reactions were stopped and worked up after 1 h by conventional procedures.[4] Crude reaction yields were determined by ^1H NMR and were found to be quantitative. The results are given in Table I.

General Procedure for the Reduction of the Olefin Esters. The procedure was the same as above except that the reactions were run in the absence of Et_3N. The results are given in Table I.

(11) Prepared as previously described.[4]

Oxidation of Uric Acid. 1. Structural Revision of Uric Acid Glycols

Mirko Poje,* Erich F. Paulus,[1a] and Boris Ročić[1b]

Department of Organic Chemistry and Biochemistry, Faculty of Science, University of Zagreb, Strossmayerov trg 14, 41000 Zagreb, Yugoslavia

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A reinvestigation of the chemistry of uric acid glycols (**2**) originally described by Biltz was made. On the basis of degradative evidence and infrared spectral characteristics, previously accepted structure **2** was revised, and the 4-hydroxy-2,5-dioxo-4-imidazolidinecarboxyureide (**4**) structure was assigned to these compounds. An unambiguous proof for the new formulation was obtained by the X-ray crystallographic study of the hemihydrate **4a**.

Summarizing the investigations on the oxidation of uric acid (**1a**),[2] Biltz in 1921 suggested that the first step is an oxidation at the double bond, leading to the intermediate glycol **2**.[3] In an effort to solve this intriguing problem, Biltz and co-workers investigated the reaction of alloxan (**3**) with ureas,[4] initially studied by Mulder,[5] and prepared identical products by oxidation of **1**,[6] assigning the structure **2** to these compounds.

A provocative hypothesis, however, that alloxan-like metabolites formed in vivo from **1a** may be involved in the etiology of diabetes mellitus gave an impetus for the reexamination of these compounds.[7]

We now wish to report the reinvestigation of the chemistry of alloxan-like compounds, revising previously accepted structure **2**. The reaction of alloxan (**3**) with urea under various experimental conditions[4,5,8] provided the necessary data for solving this structural problem. In accordance with Biltz's observations,[4c] product **4a**, mp 167–168 °C dec, is formed best by the reaction of an excess of urea with **3** in the presence of bromine and analyses for a hemihydrate $C_5H_6N_4O_5 \cdot {}^1/_2H_2O$. Its infrared spectrum in potassium bromide showed a sharp peak at 1808 cm^{-1}, along with three intense absorption bands in the 1780–1700-cm^{-1} region, characteristic of the hydantoin ring. The mass spectrum of **4a** showed no molecular ion at *m/e* 202, and only the fragment due to loss of water appeared at *m/e* 184. From the occurrence of significant metastable peaks at *m/e* 132.4, 108.1, and 90.6, it follows that the subsequent loss of CO and HNCO from *m/e* 184 gave fragments at *m/e* 156 and 141, respectively. The elimination of CO from *m/e* 141 gave ion at *m/e* 113.

The hemihydrate **4a** is smoothly dehydrated by treatment with acetic anhydride,[8] and subsequent heating with trifluoroacetic anhydride afforded spirodihydantoin **5**. The infrared spectra of **4a** and **5** showed similar features; a sharp absorption band at 1804 cm^{-1} characteristic of the hydantoin system was also present in the spectrum of **5**. The mass spectrum exhibited a fragmentation pattern similar to that of **4a**; *m/e* 184 ($M^{+\cdot}$) → *m/e* 156, and *m/e*

(1) (a) Angewandte Physik, Hoechst AG, 6230 Frankfurt (M) 80, Germany. (b) Institute for Diabetes, University of Zagreb, Krijesnice b.b., 41000 Zagreb, Yugoslavia.

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(5) E. Mulder, *Chem. Ber.*, **6**, 1010 (1873).

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